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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,355	GANTIER ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67 and 79-89* is/are pending in the application.

4a) Of the above claim(s) *12,13,19-27,39-50,56-67 and 82-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15-18,28-38,51-55 and 79-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____; 11/9/04; 1/4/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1/2/05; 11/9/05; 1/4/06; 3/14/04

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I and Specie I-A in the reply filed on February 16, 2006 is acknowledged. The traversal of the Species election is found to be persuasive due to arguments made by the applicant on pages 11-13 of the remarks of February 16, 2006. The subspecies (i.e. "activity" vs. "stability," etc.) has not been traversed by the applicant, so while Specie I-A will be rejoined with Specie I-B, the Office action will consider protein stability where the predetermined property is increased resistance to a protease. Claims 1-11, 15-18, 28-38, 51-55, and 79-81 are examined in this Office action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-13, 19-27, 39-50, 56-67, and 82-89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group or specie, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 16, 2006.

Information Disclosure Statement

The information disclosure statement filed March 17, 2004 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the

information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the patent literature referred to therein has not been considered.

Specifically, the IDS of March 17, 2004 lacks the list of patent numbers for United States for reference codes A through E.

The Information Disclosure Statement filed November 9, 2004 does not contain a legible copy of each reference listed on the list of references. It is not known whether this is an error of the applicants or a scanning error by the Office. Consequently the missing references have been listed as not considered in the signed copy of the list of references attached to this Office action. If the applicants provide a legible copy of the missing references in response to this Office action, the references will be considered under 37 CFR 1.97(f), and a signed copy of the list of references indicating consideration of the missing references will be provided to the applicants without the necessity of the applicants filing a second Information Disclosure Statement.

The missing references on the disclosure statement of November 9, 2004 are reference codes numbered "BP" and "CO."

Additionally, the information disclosure statement of November 9, 2004 has the following informalities:

The publication date of reference "AZ" is not November 15, 2001, but instead is March 11, 1999.

Reference "DR" does not have a date or relevant book or journal title information on it.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it does not mean the range of wording required (the abstract is less that 50 words in length). Additionally, it does not give a substantive definition and summary of the information included in the disclosure. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities:

On page 1, lines 15 and 18, attorney docket numbers 37851-923PC and 37851-922 are used respectively without indicating the relevant application numbers.

On page 5, line 28, the term amino acids is combined into one word.

On page 40, line 28, the full application number is not utilized (i.e. "Serial No. "922"). The full U.S. Application Number should be utilized.

Appropriate correction is required.

Drawings

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). See for example, Figures 6 and 12. However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because Figures 6 and 12 do not have SEQ ID NOs cited along with each sequence in the specification or the Figures. Applicants are also reminded that SEQ ID NOs are not required in the Figures per se, however, the corresponding SEQ ID NOs then are required in the brief description of the Drawings section in the specification. Applicants are also reminded that the CD-ROM sequence listing submission may replace the paper and computer readable form, sequence listing, a paper copy for the specification, statements under 37 C.F.R. § 1.821(f) and (g). Applicants are given the same response time regarding this failure to comply as that set forth to respond to this office action. A complete response to this office action includes compliance with this sequence rule compliance requirement. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 15-18, and 28-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, independent claims 1 and 28, contains the requirement, "each LEAD protein in a set contains the same amino acid replacement." It is unclear as to whether the applicant means that the same amino acid in each of the LEAD proteins is replaced at the same amino acid position, or if all of the LEADs have replacements with the same amino acid type. Hence, it needs to be clarified as to if it is the position on the amino acid chain or the type of amino acid that is conserved. For purposes of examination, it is assumed that the identity of the replaced amino acid remains constant.

Claim 80 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Although the term "pseudo wild type amino acid" in claim 80 is mentioned in the specification in Example 4, it is unclear as to the definition of such a term to one of ordinary skill in the art. Applicant needs to be more specific in terms of a definition of this term so that the claim is clearly understood.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-11, 28-35, and 51-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Ladner et al. [USPAT 5,096,815]

Claims 1, 4-11, 28-35, and 51-52 state:

1. A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:
(a) identifying, within a target protein or peptide, one or more target amino acids amenable to providing the evolved predetermined property or activity upon amino acid replacement, wherein each target amino acid is designated an in silico-HIT (is-HIT);
(b) identifying, one or more replacement amino acids, specific for each is-HIT, amenable to providing the evolved predetermined property or activity to the target protein upon amino acid replacement, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;
(c) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein: each candidate LEAD protein contains a single amino acid replacement; each nucleic acid in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide; each set is separate from all other sets;
(d) individually introducing each set of nucleic acid molecules into a host cells and expressing the encoded candidate LEAD proteins to produce sets of LEAD proteins, wherein: the host cells are in an addressable array such that each lead protein is expressed at a different locus in the array; and
each LEAD protein in a set contains the same amino acid replacement
(e) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such identified proteins is designated a LEAD mutant protein.

4. The method of claim 1, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids or are bacterial cells are transformed with the plasmids.

5. The method of claim 1, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

6. The method of claim 1, further comprising: (f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins; (g) introducing

each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and (h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

7. The method of claim 6, wherein the nucleic acid molecules in step (f) are produced by a method selected from among Additive Directional Mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and de novo synthesis.

8. The method of claim 1 wherein the is-HITs identified in step (a) correspond to a restricted subset of amino acids along the full length target protein.

9. The method of claim 1, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

10. The method of claim 1, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

11. The method of claim 6, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

28. A method for generating proteins with a desired property or activity, comprising:
(a) identifying a target protein;
(b) identifying is-HIT target residues associated with the property;
(c) preparing a collection of variant nucleic acid molecules encoding a collection of variant proteins, wherein each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid from the target protein at one is-HIT target residue;
(d) separately introducing the nucleic acids encoding each candidate LEAD protein into hosts for expression thereof and expressing the nucleic acid molecules encoding each variant protein to produce sets of LEAD proteins, wherein each LEAD protein in a set contains the same amino acid replacement;
(e) screening each set of variant LEAD candidate proteins to identify any that have an activity or property that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

29. The method of claim 28, wherein either: each of the identified is-HIT target residues in the target protein is replaced with codons encoding a restricted subset of the

remaining 19 amino acids; or the total number of is-HIT residues that are replaced with replacement amino acids is less than the total amount of amino acid residues within the full-length of the target protein.

30. The method of claim 28, wherein each of the identified is-HIT residues in the target protein is replaced with codons encoding a restricted subset of the remaining 19 amino acids.

31. The method of claim 28, wherein the total number of is-HIT residues that are replaced with replacement amino acids is less than the total amount of amino acid residues within the full-length of the target protein.

32. The method of claim 28, wherein each of the identified is-HIT residues in the target protein is replaced with codons encoding a restricted subset of the remaining 19 amino acids; and the total number of is-HIT residues that are replaced with replacement amino acids is less than the total amount of amino acid residues within the full-length of the target protein.

33. The method of claim 28, further comprising:
(f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;
(g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and
(h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

34. The method of claim 33, wherein the nucleic acid molecules in step (f) are produced by a method selected from among additive directional mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and de novo synthesis.

35. The method of claim 33, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

51. A method for the production of a protein having an evolved property or activity compared to a unmodified target protein, the method comprising:
(a) selecting, on the target protein, one or more target amino acids amenable to providing the evolved property or activity upon amino acid replacement;

(b) replacing each target amino acid with a replacement amino acid amenable to providing the evolved property or activity to form a candidate LEAD protein, wherein only one amino acid replacement occurs on each target protein;
(c) expressing from a nucleic acid molecule each candidate LEAD protein in a cell contained in an addressable array; and
(d) individually assaying each candidate LEAD protein for the presence or absence of the evolved property or activity compared to a unmodified target protein, thereby identifying proteins that are LEADs.

52. The method of claim 51, wherein the selection of the one or more target amino acids in step a) is conducted in silico and the targets amino acids are designated is-Hits.

The patent of Ladner et al, entitled, "Generation and selection of novel DNA-binding proteins and polypeptides, states in its abstract, "Novel DNA-binding proteins, especially repressors of gene expression, are obtained by variegation of genes encoding known binding protein and selection for protein binding the desired target DNA sequence."

The computational modeling aspect of the sites for mutagenesis on the proteins are described in the Graphical and Computational Tools section in column 62, line 56 to column 63, line 11 and column 63, lines 25-34, which state, "The most appropriate method of picking the residues of the protein chain at which the amino acids should be varied is by viewing with interactive computer graphics a model of the initial DBP complexed with operator DNA. This model need not come from an X-ray ray [sic] structure of the complex, but could instead be obtained by docking a 3D structure of the initial DBP to an appropriate model of the DNA operator sequence. A model based on X-ray data from the DNA-protein complex is preferred. A stick figure representation of molecules is preferred. A suitable set of hardware is an Evans & Sutherland PS390 graphics terminal ... and a MicroVAX II supermicro computer... The computer model

should preferably have at least 150 megabytes of disk storage, so that the Brookhaven Protein Data Bank can be kept on line. A FORTRAN compiler, or some equally good higher-level language processor is preferred for program development..."

Column 63, lines 25-34 state, "In addition, one could use theoretical calculations, such as dynamic simulations of proteins, DNA, or protein-DNA complexes to estimate whether a substitution at a particular residue of a particular amino acid type might produce a protein of approximately the same 3D structure as the parent protein. Such calculations might also indicate whether a particular substitution will greatly affect the flexibility of the protein; calculations of this sort may be useful but are not required."

Empirical methods are described in column 12, lines 50-79, of Ladner et al. which state, "This application uses the term 'variegated DNA' to refer to a population of molecules that have the same base sequence through most of their length, but that vary at a number of defined loci... When plasmids containing the variegated DNA are used to transform bacteria, each cell makes a version of the original protein. Each colony of bacteria produces a different version from most other colonies. If the variegations of the DNA are concentrated at loci that code on expression for residues known to be on the surface of the protein or in the loops, a population of genes will be generated that code on expression for a population of proteins, many members of which will fold roughly the same 3D structure as the parental protein. Most often we generate mutations that are concentrated within the codons for residues thought to make contact with the DNA."

Empirical methods and assays (which further define a restricted set of "focused" mutations) are further described in columns 77, line 66 to column 78, line 5 of Ladner et

al which states, "The initial set of 5 residues for Focused Mutagenesis contains residues in or near the N-terminal half of alpha helix 3: Y26, Q27, S28, N31, and K32. Varying these 5 residues through all 20 amino acids produces 3.2×10^6 different protein sequences encoded by 32^5... different DNA sequences. Since all 5 residues are in the same interaction set, the variegation scheme produces the maximum number of different surfaces." Ladner et al. continue in column 78, lines 17-30 by stating, "We synthesize DNA inserts having approximate level of variegation, ligate the synthetic DNA into appropriately digested and purified plasmid DNA, transform competent cells, select for uptake of plasmid, introduce the cells for production of potential DBPs [DNA Binding Proteins], and then select for the wanted DNA binding phenotype using the binding marker genes. Surviving colonies are screened genetically and biochemically to verify that a novel DBP is effectively binding to the target DNA sequence. DBP characterization includes, at the genetic level, deleting and back-crossing the dbp gene at the protein level, in vitro binding assays; and, at the DNA level, determination of the complete sequence of the dbp gene."

Thus, a method for generating a protein or peptide molecule is discussed. Target amino acids are identified by computer, and candidate substitutions are identified. A collection of mutants with desired properties are produces. They are expressed by genes in plasmids in host bacteria, and they are finally screened. This is a process of site-specific mutagenesis at the restricted sited of 5 specific residues. LEAD (single mutation) and super-LEAD (multiple mutation) proteins are produced and screened with in the 3.2×10^6 different protein sequences corresponding to all 20

occurring amino acids. Codons of the genes in the plasmids are altered to result in the mutated proteins. The specific number of amino acids investigated was 5.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 15-18, 28, 36-38, 52-55, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. [USPAT 5,096,815] in view of Alam et al. [Journal of Biotechnology, volume 65, 1998, pages 183-190].

Claims 1, 6, 15-18, 28, 36-38, 51-55, and 81 state:

1. A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:
(a) identifying, within a target protein or peptide, one or more target amino acids amenable to providing the evolved predetermined property or activity upon amino acid replacement, wherein each target amino acid is designated an in silico-HIT (is-HIT);
(b) identifying, one or more replacement amino acids, specific for each is-HIT, amenable to providing the evolved predetermined property or activity to the target protein upon amino acid replacement, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;
(c) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein: each candidate LEAD protein contains a single amino acid replacement; each nucleic acid in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide; each set is separate from all other sets;
(d) individually introducing each set of nucleic acid molecules into a host cells and expressing the encoded candidate LEAD proteins to produce sets of LEAD proteins, wherein: the host cells are in an addressable array such that each lead protein is expressed at a different locus in the array; and
each LEAD protein in a set contains the same amino acid replacement

(e) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such identified proteins is designated a LEAD mutant protein.

6. The method of claim 1, further comprising: (f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins; (g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and (h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

15. The method of claim 1, wherein the activity modified is selected from among increased catalytic activity, altered substrate and ligand recognition, increased thermostability, increased stability, increased resistance to proteases, increased resistance to glomerular filtration, increased immunogenicity, increased cationization, increased anionization and pseudo wild-type function.

16. The method of claim 1, wherein each is-HIT target amino acid is susceptible to digestion by one or more proteases.

17. The method of claim 16, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

18. The method of claim 1, wherein in a modified protein, each is-HIT target amino acid is resistant to digestion by one or more proteases compared to in unmodified protein.

28. A method for generating proteins with a desired property or activity, comprising:
(a) identifying a target protein;
(b) identifying is-HIT target residues associated with the property;
(c) preparing a collection of variant nucleic acid molecules encoding a collection of variant proteins, wherein each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid from the target protein at one is-HIT target residue;
(d) separately introducing the nucleic acids encoding each candidate LEAD protein into hosts for expression thereof and expressing the nucleic acid molecules encoding each variant protein to produce sets of LEAD proteins, wherein each LEAD protein in a set contains the same amino acid replacement;
(e) screening each set of variant LEAD candidate proteins to identify any that have an activity or property that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

36. The method of claim 28, wherein each is-HIT target residue is susceptible to digestion by one or more proteases.

37. The method of claim 36, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

38. The method of claim 28, wherein each is-HIT target residue is resistant to digestion by one or more proteases.

51. A method for the production of a protein having an evolved property or activity compared to a unmodified target protein, the method comprising:
(a) selecting, on the target protein, one or more target amino acids amenable to providing the evolved property or activity upon amino acid replacement;
(b) replacing each target amino acid with a replacement amino acid amenable to providing the evolved property or activity to form a candidate LEAD protein, wherein only one amino acid replacement occurs on each target protein;
(c) expressing from a nucleic acid molecule each candidate LEAD protein in a cell contained in an addressable array; and
(d) individually assaying each candidate LEAD protein for the presence or absence of the evolved property or activity compared to a unmodified target protein, thereby identifying proteins that are LEADs.

52. The method of claim 51, wherein the selection of the one or more target amino acids in step a) is conducted in silico and the targets amino acids are designated is-Hits.

53. The method of claim 52, wherein the in silico selection step further comprises selecting an is-HIT target residue that is susceptible to digestion by one or more proteases.

54. The method of claim 53, wherein the LEADs possess increased resistance to proteolysis compared to unmodified target protein.

55. The method of claim 52, wherein the in silico selection step further comprises selecting an is-HIT target residue that is resistant to digestion by one or more proteases.

81. The method of claim 6, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

The patent of Ladner et al, entitled, "Generation and selection of novel DNA-binding proteins and polypeptides, states in its abstract, "Novel DNA-binding proteins,

especially repressors of gene expression, are obtained by variegation of genes encoding known binding protein and selection for protein binding the desired target DNA sequence."

The computational modeling aspect of the sites for mutagenesis on the proteins are described in the Graphical and Computational Tools section in column 62, line 56 to column 63, line 11 and column 63, lines 25-34, which state, "The most appropriate method of picking the residues of the protein chain at which the amino acids should be varied is by viewing with interactive computer graphics a model of the initial DBP complexed with operator DNA. This model need not come from an X-ray ray [sic] structure of the complex, but could instead be obtained by docking a 3D structure of the initial DBP to an appropriate model of the DNA operator sequence. A model based on X-ray data from the DNA-protein complex is preferred. A stick figure representation of molecules is preferred. A suitable set of hardware is an Evans & Sutherland PS390 graphics terminal ... and a MicroVAX II supermicro computer... The computer model should preferably have at least 150 megabytes of disk storage, so that the Brookhaven Protein Data Bank can be kept on line. A FORTRAN compiler, or some equally good higher-level language processor is preferred for program development..."

Column 63, lines 25-34 state, "In addition, one could use theoretical calculations, such as dynamic simulations of proteins, DNA, or protein-DNA complexes to estimate whether a substitution at a particular residue of a particular amino acid type might produce a protein of approximately the same 3D structure as the parent protein. Such

calculations might also indicate whether a particular substitution will greatly affect the flexibility of the protein; calculations of this sort may be useful but are not required."

Empirical methods are described in column 12, lines 50-79, of Ladner et al. which state, "This application uses the term 'variegated DNA' to refer to a population of molecules that have the same base sequence through most of their length, but that vary at a number of defined loci... When plasmids containing the variegated DNA are used to transform bacteria, each cell makes a version of the original protein. Each colony of bacteria produces a different version from most other colonies. If the variegations of the DNA are concentrated at loci that code on expression for residues known to be on the surface of the protein or in the loops, a population of genes will be generated that code on expression for a population of proteins, many members of which will fold roughly the same 3D structure as the parental protein. Most often we generate mutations that are concentrated within the codons for residues thought to make contact with the DNA."

Empirical methods and assays (which further define a restricted set of "focused" mutations) are further described in columns 77, line 66 to column 78, line 5 of Ladner et al which states, "The initial set of 5 residues for Focused Mutagenesis contains residues in or near the N-terminal half of alpha helix 3: Y26, Q27, S28, N31, and K32. Varying these 5 residues through all 20 amino acids produces 3.2×10^6 different protein sequences encoded by 32^5... different DNA sequences. Since all 5 residues are in the same interaction set, the variegation scheme produces the maximum number of different surfaces." Ladner et al. continue in column 78, lines 17-30 by stating, "We synthesize DNA inserts having approximate level of variegation, ligate the synthetic

DNA into appropriately digested and purified plasmid DNA, transform competent cells, select for uptake of plasmid, introduce the cells for production of potential DBPs [DNA Binding Proteins], and then select for the wanted DNA binding phenotype using the binding marker genes. Surviving colonies are screened genetically and biochemically to verify that a novel DBP is effectively binding to the target DNA sequence. DBP characterization includes, at the genetic level, deleting and back-crossing the dbp gene at the protein level, in vitro binding assays; and, at the DNA level, determination of the complete sequence of the dbp gene."

Thus, a method for generating a protein or peptide molecule is discussed. Target amino acids are identified by computer, and candidate substitutions are identified. A collection of mutants with desired properties are produces. They are expressed by genes in plasmids in host bacteria, and they are finally screened. This is a process of site-specific mutagenesis at the restricted sited of 5 specific residues. LEAD (single mutation) and super-LEAD (multiple mutation) proteins are produced and screened with in the 3.2×10^6 different protein sequences corresponding to all 20 occurring amino acids. Codons of the genes in the plasmids are altered to result in the mutated proteins. The specific number of amino acids investigated was 5.

However, Ladner et al. does not teach increased resistance to proteolysis as a result of mutations.

In the article of Alam et al., entitled, "Expression and purification of a mutant human growth hormone that it resistant to proteolytic cleavage by thrombin, plasmin and human plasma in vitro," Alam et al. take a section of human growth hormone which

is not resistant to proteolysis, and conduct mutations to the hormone to make it resistant to proteolysis (see for instant, abstract on page 183 which states, "In this study, oligonucleotide primer-directed mutagenesis was used to produce recombinant mutant hGHs resistant to limited proteolysis by these proteases.")

Thus, it would have been obvious to someone or ordinary skill in the art at the time of the instant invention to practice Ladner et al. in view of Alam et al. to result in the instantly claimed invention because Alam et al. has the advantage of applying the site directed mutagenesis study of Ladner et al. to the claimed condition of mutation to make resistant to proteolysis.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. [USPAT 5,096,815] in view of Chiang et al. [Annual Reviews of Microbiology, 1999, volume 53, pages 129-154].

Claims 1-3 state:

1. A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:
(a) identifying, within a target protein or peptide, one or more target amino acids amenable to providing the evolved predetermined property or activity upon amino acid replacement, wherein each target amino acid is designated an in silico-HIT (is-HIT);
(b) identifying, one or more replacement amino acids, specific for each is-HIT, amenable to providing the evolved predetermined property or activity to the target protein upon amino acid replacement, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;
(c) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein: each candidate LEAD protein contains a single amino acid replacement; each nucleic acid in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide; each set is separate from all other sets;
(d) individually introducing each set of nucleic acid molecules into a host cells and expressing the encoded candidate LEAD proteins to produce sets of LEAD proteins, wherein: the host cells are in an addressable array such that each lead protein is expressed at a different locus in the array; and

each LEAD protein in a set contains the same amino acid replacement
(e) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such identified proteins is designated a LEAD mutant protein.

2. The method of claim 1, wherein the array comprises a solid support with separate loci and each set of cells is at a different locus.

3. The method of claim 2, wherein the loci comprise wells; and each well contains one set of cells.

The patent of Ladner et al, entitled, "Generation and selection of novel DNA-binding proteins and polypeptides, states in its abstract, "Novel DNA-binding proteins, especially repressors of gene expression, are obtained by variegation of genes encoding known binding protein and selection for protein binding the desired target DNA sequence."

The computational modeling aspect of the sites for mutagenesis on the proteins are described in the Graphical and Computational Tools section in column 62, line 56 to column 63, line 11 and column 63, lines 25-34, which state, "The most appropriate method of picking the residues of the protein chain at which the amino acids should be varied is by viewing with interactive computer graphics a model of the initial DBP complexed with operator DNA. This model need not come from an X-ray ray [sic] structure of the complex, but could instead be obtained by docking a 3D structure of the initial DBP to an appropriate model of the DNA operator sequence. A model based on X-ray data from the DNA-protein complex is preferred. A stick figure representation of molecules is preferred. A suitable set of hardware is an Evans & Sutherland PS390 graphics terminal ... and a MicroVAX II supermicro computer... The computer model should preferably have at least 150 megabytes of disk storage, so that the Brookhaven

Protein Data Bank can be kept on line. A FORTRAN compiler, or some equally good higher-level language processor is preferred for program development..."

Column 63, lines 25-34 state, "In addition, one could use theoretical calculations, such as dynamic simulations of proteins, DNA, or protein-DNA complexes to estimate whether a substitution at a particular residue of a particular amino acid type might produce a protein of approximately the same 3D structure as the parent protein. Such calculations might also indicate whether a particular substitution will greatly affect the flexibility of the protein; calculations of this sort may be useful but are not required."

Empirical methods are described in column 12, lines 50-79, of Ladner et al. which state, "This application uses the term 'variegated DNA' to refer to a population of molecules that have the same base sequence through most of their length, but that vary at a number of defined loci... When plasmids containing the variegated DNA are used to transform bacteria, each cell makes a version of the original protein. Each colony of bacteria produces a different version from most other colonies. If the variegations of the DNA are concentrated at loci that code on expression for residues known to be on the surface of the protein or in the loops, a population of genes will be generated that code on expression for a population of proteins, many members of which will fold roughly the same 3D structure as the parental protein. Most often we generate mutations that are concentrated within the codons for residues thought to make contact with the DNA."

Empirical methods and assays (which further define a restricted set of "focused" mutations) are further described in columns 77, line 66 to column 78, line 5 of Ladner et al which states, "The initial set of 5 residues for Focused Mutagenesis contains residues

in or near the N-terminal half of alpha helix 3: Y26, Q27, S28, N31, and K32. Varying these 5 residues through all 20 amino acids produces 3.2×10^6 different protein sequences encoded by 32^5... different DNA sequences. Since all 5 residues are in the same interaction set, the variegation scheme produces the maximum number of different surfaces." Ladner et al. continue in column 78, lines 17-30 by stating, "We synthesize DNA inserts having approximate level of variegation, ligate the synthetic DNA into appropriately digested and purified plasmid DNA, transform competent cells, select for uptake of plasmid, introduce the cells for production of potential DBPs [DNA Binding Proteins], and then select for the wanted DNA binding phenotype using the binding marker genes. Surviving colonies are screened genetically and biochemically to verify that a novel DBP is effectively binding to the target DNA sequence. DBP characterization includes, at the genetic level, deleting and back-crossing the dbp gene at the protein level, in vitro binding assays; and, at the DNA level, determination of the complete sequence of the dbp gene."

Thus, a method for generating a protein or peptide molecule is discussed. Target amino acids are identified by computer, and candidate substitutions are identified. A collection of mutants with desired properties are produces. They are expressed by genes in plasmids in host bacteria, and they are finally screened. This is a process of site-specific mutagenesis at the restricted sited of 5 specific residues. LEAD (single mutation) and super-LEAD (multiple mutation) proteins are produced and screened with in the 3.2×10^6 different protein sequences corresponding to all 20

occurring amino acids. Codons of the genes in the plasmids are altered to result in the mutated proteins. The specific number of amino acids investigated was 5.

However, Ladner et al. do not teach use of solid support with wells to analyze each specie of protein.

In the article of Chiang et al., "In vivo genetic analysis of bacterial virulence," Chiang et al state on page 138, last full paragraph, "mutagenized bacterial strains are stored individually in arrays (usually in the wells of microtiter dishes)..."

Thus, it would have been obvious to someone or ordinary skill in the art at the time of the instant invention to practice Ladner et al. in view of Chiang et al. to result in the instantly claimed invention because Chiang et al. has the advantage of applying the site directed mutagenesis study of Ladner et al. to the claimed condition of wells on a solid support.

Claims 1 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. [USPAT 5,096,815] in view of Jones et al. [CABIOS, volume 8, 1992, pages 275-282].

Claims 1and 79 state:

1. A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:
(a) identifying, within a target protein or peptide, one or more target amino acids amenable to providing the evolved predetermined property or activity upon amino acid replacement, wherein each target amino acid is designated an in silico-HIT (is-HIT);
(b) identifying, one or more replacement amino acids, specific for each is-HIT, amenable to providing the evolved predetermined property or activity to the target protein upon amino acid replacement, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;
(c) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein: each candidate LEAD protein contains a single amino acid replacement; each nucleic acid in a set encodes the same candidate LEAD

protein that differs by one amino acid from the target protein or peptide; each set is separate from all other sets;
(d) individually introducing each set of nucleic acid molecules into a host cells and expressing the encoded candidate LEAD proteins to produce sets of LEAD proteins, wherein: the host cells are in an addressable array such that each lead protein is expressed at a different locus in the array; and
each LEAD protein in a set contains the same amino acid replacement
(e) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such identified proteins is designated a LEAD mutant protein.

79. The method of claim 1, wherein the replacement amino acids are selected using Percent Accepted Mutations (PAM) matrices.

The patent of Ladner et al, entitled, "Generation and selection of novel DNA-binding proteins and polypeptides, states in its abstract, "Novel DNA-binding proteins, especially repressors of gene expression, are obtained by variegation of genes encoding known binding protein and selection for protein binding the desired target DNA sequence."

The computational modeling aspect of the sites for mutagenesis on the proteins are described in the Graphical and Computational Tools section in column 62, line 56 to column 63, line 11 and column 63, lines 25-34, which state, "The most appropriate method of picking the residues of the protein chain at which the amino acids should be varied is by viewing with interactive computer graphics a model of the initial DBP complexed with operator DNA. This model need not come from an X-ray ray [sic] structure of the complex, but could instead be obtained by docking a 3D structure of the initial DBP to an appropriate model of the DNA operator sequence. A model based on X-ray data from the DNA-protein complex is preferred. A stick figure representation of molecules is preferred. A suitable set of hardware is an Evans & Sutherland PS390

graphics terminal ... and a MicroVAX II supermicro computer... The computer model should preferably have at least 150 megabytes of disk storage, so that the Brookhaven Protein Data Bank can be kept on line. A FORTRAN compiler, or some equally good higher-level language processor is preferred for program development..."

Column 63, lines 25-34 state, "In addition, one could use theoretical calculations, such as dynamic simulations of proteins, DNA, or protein-DNA complexes to estimate whether a substitution at a particular residue of a particular amino acid type might produce a protein of approximately the same 3D structure as the parent protein. Such calculations might also indicate whether a particular substitution will greatly affect the flexibility of the protein; calculations of this sort may be useful but are not required."

Empirical methods are described in column 12, lines 50-79, of Ladner et al. which state, "This application uses the term 'variegated DNA' to refer to a population of molecules that have the same base sequence through most of their length, but that vary at a number of defined loci... When plasmids containing the variegated DNA are used to transform bacteria, each cell makes a version of the original protein. Each colony of bacteria produces a different version from most other colonies. If the variegations of the DNA are concentrated at loci that code on expression for residues known to be on the surface of the protein or in the loops, a population of genes will be generated that code on expression for a population of proteins, many members of which will fold roughly the same 3D structure as the parental protein. Most often we generate mutations that are concentrated within the codons for residues thought to make contact with the DNA."

Empirical methods and assays (which further define a restricted set of "focused" mutations) are further described in columns 77, line 66 to column 78, line 5 of Ladner et al which states, "The initial set of 5 residues for Focused Mutagenesis contains residues in or near the N-terminal half of alpha helix 3: Y26, Q27, S28, N31, and K32. Varying these 5 residues through all 20 amino acids produces 3.2×10^6 different protein sequences encoded by 32^5... different DNA sequences. Since all 5 residues are in the same interaction set, the variegation scheme produces the maximum number of different surfaces." Ladner et al. continue in column 78, lines 17-30 by stating, "We synthesize DNA inserts having approximate level of variegation, ligate the synthetic DNA into appropriately digested and purified plasmid DNA, transform competent cells, select for uptake of plasmid, introduce the cells for production of potential DBPs [DNA Binding Proteins], and then select for the wanted DNA binding phenotype using the binding marker genes. Surviving colonies are screened genetically and biochemically to verify that a novel DBP is effectively binding to the target DNA sequence. DBP characterization includes, at the genetic level, deleting and back-crossing the dbp gene at the protein level, in vitro binding assays; and, at the DNA level, determination of the complete sequence of the dbp gene."

Thus, a method for generating a protein or peptide molecule is discussed. Target amino acids are identified by computer, and candidate substitutions are identified. A collection of mutants with desired properties are produces. They are expressed by genes in plasmids in host bacteria, and they are finally screened. This is a process of site-specific mutagenesis at the restricted sited of 5 specific residues.

LEAD (single mutation) and super-LEAD (multiple mutation) proteins are produced and screened with in the 3.2 x 10^6 different protein sequences corresponding to all 20 occurring amino acids. Codons of the genes in the plasmids are altered to result in the mutated proteins. The specific number of amino acids investigated was 5.

However, Ladner et al. do not teach PAM matrices.

Jones et al. show PAM matrices on Table I on page 279 for the purpose of mutation of protein sequences.

Thus, it would have been obvious to someone or ordinary skill in the art at the time of the instant invention to practice Ladner et al. in view of Jones et al. to result in the instantly claimed invention because Jones et al. has the advantage of applying the site directed mutagenesis study of Ladner et al. to the claimed analysis condition of PAM matrices.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Regarding use of the specification in obviousness-type double patenting rejections, the MPEP states in section 804:

When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.

The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Claims 1, 4-11, 15, and 79-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 250, 251, 256-264, and 268-269 of copending Application No. 10/658,834. Although the conflicting claims are not identical, they are not patentably distinct from each other because while the claims of the reference are generic to the instant application, the

specification of the reference specifically discloses the species employed in the claims of the instant application.

The two main issues are the facts that in the independent claim (claim 1): (1) each set of nucleic acid molecules in the instant application are *individually* introduces into host cells and (2) each LEAD protein in a set contains the same amino acid replacement. These species are disclosed in paragraphs [0149] and [0130] of the reference specification which states [0149], "As used herein, a population of sets of nucleic acid molecules encoding a collection (library) of mutants refers to a collection of plasmids or other vehicles that carry (encode) the gene variants, such that individual plasmids or other individual vehicles carry individual gene variants. Each element (member) of the collection is physically separated from the others, such as individually in an appropriate addressable array, and has been generated as the single product of an independent mutagenesis reaction." Paragraph [0130] states, "Thus, a plurality of mutant protein molecules are produced, whereby each mutant protein contains a single amino acid replacement at only one of the is-HIT target positions." Thus, while individual replacements are introduced into host cells, each LEAD protein in a set contains the same amino acid replacement.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by,

or would be obvious over, the reference claim(s). see, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(f) he did not himself invent the subject matter sought to be patented.

Claims 1, 4-11, 15, and 79-81 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

For the reasons discussed above, it is apparent that copending Application No. 10/658,834 contains claimed subject matter in claims that is not patentably distinct from instant claims 1, 4-11, 15, and 79-81. Because the inventive entity of copending Application is different from the instant application, a rejection is appropriate under 35 U.S.C. 102(f). This rejection could be overcome by amendment of the appropriate claims so that the claims are patentably distinct, or by filing a declaration stating the inventive entity for the commonly claimed subject matter is identical.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Ardin Marschel, Ph.D., Supervisory Patent Examiner, can be reached at (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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4/30/06

30 August 2006

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PRIMARY EXAMINER